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Health Effects Assessment for 2-Chlorophenol and 2,4-Dichlorophenol

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HEALTH EFFECTS ASSESSMENT FOR 2-CHLOROPHENOL AND 2,4-DICHLOROPHENOL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with selected chlorinated phenols. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary reflecting limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1979a. Review of the Environmental Effects of Pollutants. XI. Chlorophenols. Office of Research and Development, Health Effects Research Laboratory, U.S. EPA, Cincinnati, OH. EPA 600/1-79-012.

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for 2-Chlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-034. NTIS PB81-117459.

U.S. EPA. 1980b. Ambient Water Quality Criteria Document for 2,4-Dichlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 400/5-80-042. NTIS PB81-117533.

U.S. EPA. 1980c. Hazard Profile for Chlorinated Phenols. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1983a. Reportable Quantity Document for 2-Chlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1983b. Reportable Quantity Document for 2,4-Dichlorophenol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RfD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980d) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980d). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Data were located only for oral exposure to 2-chlorophenol and 2,4-dichlorophenol. An RfD_0 and RfD_{S0} for exposure to 2-chlorophenol of 0.35 mg/day was derived from a NOAEL of 50 ppm for reproductive effects in a subchronic drinking water study using rats (Exon and Koller, 1982). A CS of 10.4 was derived for effects on reproduction in rats at 500 ppm, the next higher level in the same study.

For 2,4-dichlorophenol, an RfD_{S0} value of 0.2 mg/day for oral exposure was derived from a NOAEL of 3 ppm in a 15-week drinking water study in rats (Exon and Koller, 1985). Since the test animals were exposed both in utero and through milk before the 15-week administration in drinking water, an additional factor for use of subchronic study was not considered necessary. Therefore, an RfD_0 of 0.2 mg/day was derived. A CS of 11.9 was associated with mild histopathological lesions in the livers of mice exposed to 2,4-dichlorophenol in the diet for 6 months (Kobayashi et al., 1972; U.S. EPA, 1983b).

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
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Office of Drinking Water

Editorial review for the document series was provided by the following:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by the following:

Bette Zwayer, Jacky Bohanon and Kim Davidson
Environmental Criteria and Assessment Office
Cincinnati, OH

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LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
DMBA	Dimethyl benzanthracene
DWEL	Drinking water equivalent level
K_{oc}	Soil sorption coefficient
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value

1. ENVIRONMENTAL CHEMISTRY AND FATE

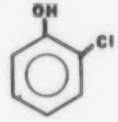
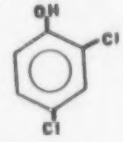
Selected chemical and physical properties and environmental fate of 2-chlorophenol (CAS No. 95-57-8) and 2,4-dichlorophenol (CAS No. 120-83-2) are presented in Table 1-1. Synonyms for 2-chlorophenol are o-chlorophenol and 1-chloro-2-hydroxybenzene.

If present in the atmosphere, 2-chlorophenol and 2,4-dichlorophenol should exist primarily in the vapor phase. The atmospheric half-lives listed in Table 1-1 are for the oxidation of vapor-phase chlorophenols by photochemically generated hydroxyl radicals. These values were calculated using estimated reaction rate constants of 5.1×10^{-12} cm³/molecule-sec for 2-chlorophenol and 1.53×10^{-12} cm³/molecule-sec for 2,4-dichlorophenol at 25°C and an ambient hydroxyl radical concentration of 8.0×10^{5} molecules/cm³ (U.S. EPA, 1986a). In water, the chlorophenols will exist in both ionic and nonionic forms, with the extent of ionization increasing with increasing pH. Biodegradation and photolysis are expected to be the important fate processes (Callahan et al., 1979). The half-life of 2,4-dichlorophenol in water (see Table 1-1) is the minimum biodegradation half-life for this compound reported by Callahan et al. (1979). Since 2,4-dichlorophenol is structurally comparable with 2-chlorophenol, the two compounds are expected to have similar half-lives. K_{oc} values of the chlorophenols suggest that adsorption to sediments would be significant, and the BCF values suggest that bioaccumulation in aquatic organisms would not be significant.

In soil, the chlorophenols appear to be removed primarily by microbial decomposition (U.S. EPA, 1980a,b; Baker et al., 1980). The soil half-lives listed above are based on the observation that 94% loss of 2-chlorophenol

TABLE 1-1

Chemical and Physical Properties and Environmental Fate for Selected Chlorinated Phenols

Property	2-Chlorophenol	2,4-Dichlorophenol	Reference
Chemical class:	halogenated phenol	halogenated phenol	
Molecular weight:	128.56	163.01	
Chemical formula:			
Melting point (°C):	8.7	43-44	Freiter, 1979
Boiling point (°C):	175-176	210-211	Freiter, 1979
Vapor pressure:	2.25 mm Hg at 20°C	0.12 mm Hg at 20°C (estimated)	Weber et al., 1981; Callahan et al., 1979
Water solubility:	28,500 mg/ℓ at 20°C	4500 mg/ℓ at 25°C	Verschueren, 1983
pKa:	8.49 at 25°C	7.68 at 25°C	U.S. EPA, 1979b
Log octanol/water partition coefficient:	2.16	3.19	U.S. EPA, 1980a,b
Bioconcentration factor:	214, bluegill sunfish (Lepomis macrochirus)	150, bluegill sunfish (Lepomis macrochirus)	Veith et al., 1980
Soil adsorption coefficient:	3990-4850	3130-3990	Isaacson and Frink, 1984
Half-lives in			
Air:	~2 days (estimated)	~7 days (estimated)	U.S. EPA, 1986a
Water:	NA	>6 days	Callahan et al., 1979
Soil:	<2 days	<5 days	Baker et al., 1980

NA = Not available

occurred in 6.5 days and 82% loss of 2,4-dichlorophenol occurred in 12 days when 119.05 µg/g soil of each compound were incubated individually under aerobic conditions at 4°C (Baker et al., 1980). The relatively high K_{oc} values of 2-chlorophenol and 2,4-dichlorophenol indicate that these compounds should have low mobility in acidic soils where hydrogen bonding is possible; however, these compound will become reasonably mobile as the pH of the soil increases (U.S. EPA, 1979a).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Quantitative absorption data on 2-chlorophenol or 2,4-dichlorophenol after oral administration were not available; however, the U.S. EPA (1980a,b) indicated that chlorophenols are readily absorbed because of their high lipid solubility and low degree of ionization at physiological pH. Gastrointestinal absorption may be inferred since hematological and reproductive toxicity were reported in rats given oral doses of 2-chlorophenol or 2,4-dichlorophenol (Chapter 3).

2.2. INHALATION

Quantitative absorption data after inhalation exposure to 2-chlorophenol or 2,4-dichlorophenol could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Conventional subchronic toxicity studies with 2-chlorophenol, in which known doses of test chemical were administered and a comprehensive set of parameters of toxicity was evaluated, could not be located in the available literature. As part of a larger study, Exon and Koller (1985) investigated the effects of pre- and postnatal exposure to 2-chlorophenol or 2,4-dichlorophenol on the immune response of Sprague-Dawley rats. Drinking water concentrations of 2-chlorophenol at 0, 5, 50 and 500 ppm or of 2,4-dichlorophenol at 0, 3, 30 and 300 ppm were provided to dams from ~3 weeks of age through parturition and lactation and to the progeny following weaning at 3 weeks. Groups of eight pups, randomly selected from among the progeny of dams treated with drinking water containing the test chemicals, were given drinking water containing these chemicals for an additional 12-15 weeks. Humoral immunity was evaluated by the enzyme-linked immunosorbent assay, cell-mediated immunity was evaluated by measuring a delayed-type hypersensitivity reaction to various antigens and macrophage function was evaluated by assessing ability to phagocytize sheep red blood cells in vitro. No statistically significant effects on immune function were noted in rats treated with 2-chlorophenol, although a consistently reduced level of humoral antibody to one antigen, bovine serum albumin, did occur in all treated groups. 2,4-Dichlorophenol seemed to enhance humoral immunity and depress cell-mediated immunity, both in a dose-related manner, and appeared to have no effect on macrophage formation. Depression of cell-mediated immunity became statistically significant at 30 ppm.

Kobayashi et al. (1972) microscopically observed "slight unfavorable changes" in the livers of male mice given 0.2% dietary 2,4-dichlorophenol for 6 months. There were no effects on behavior, growth rate, hematology or clinical chemistry at this level. The investigators measured food consumption and body weights and determined that this concentration provided 230 mg/kg/day. No changes were seen at the 0.02-0.1% dietary levels and the authors concluded that 0.1% (100 mg/kg/day) constituted a maximum no effect level. Borzelleca et al. (1985) found that mice exposed to drinking water containing 0.02-2.0 mg/mL 2,4-dichlorophenol in Emulphor for 90 days showed no consistent compound-related differences in respect to terminal body weight or absolute or relative organ weight, hematology or clinical chemistry from mice receiving Emulphor-treated water only. There were major differences, however, in hematological and clinical chemistry values, mixed function oxidase activity and organ weights, between control mice receiving Emulphor-treated water and those receiving untreated deionized water. These findings obscure the significance of the results from the 2,4-dichlorophenol-exposed mice. The investigators calculated 2,4-dichlorophenol to be 50, 143 and 491 mg/kg/day for females and 40, 114 and 383 mg/kg/day for males in the low-, middle- and high-dose groups, respectively. They concluded that Emulphor was "not without effect" in this study and that 2,4-dichlorophenol elicited no consistent treatment- or dose-related effects in this experiment.

3.1.2. Inhalation. Pertinent data regarding subchronic inhalation exposure to either 2-chlorophenol or 2,4-dichlorophenol could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. As part of a larger carcinogenicity-cocarcinogenicity study, Exon and Koller (1985) treated groups of 24-32 Sprague-Dawley

rats/sex with 0, 5, 50 or 500 ppm 2-chlorophenol or 0, 3, 30 or 300 ppm 2,4-dichlorophenol in drinking water from weaning to ~2 years of age. These rats were the progeny of dams exposed to the same treatments from 3 weeks of age through the weaning of their offspring. After 14 months, administration of the high concentration of either compound led to elevations in erythrocyte counts and hemoglobin levels. Packed cell volume was increased by 2-chlorophenol administration. Hematological effects at lower doses and other parameters of toxicity were not discussed.

3.2.2. Inhalation. Pertinent data regarding the toxicity of either 2-chlorophenol or 2,4-dichlorophenol after chronic inhalation exposure could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Exon and Koller (1985) performed a single generation reproductive study in groups of 12-14 female Sprague-Dawley rats exposed in drinking water. Concentrations of 2-chlorophenol at 0, 5, 50 and 500 ppm and of 2,4-dichlorophenol at 0, 3, 30 and 300 ppm were provided from time of weaning, through mating to untreated males at 90 days of age, and through parturition. Reproductive parameters evaluated included percent conception, litter size, number of stillborn, body weight of offspring at birth and weaning, and survival to weaning. Administration of 500 ppm 2-chlorophenol in drinking water led to decreased litter sizes and increased number of stillborn pups ($p \leq 0.10$). Lower concentrations had no effects on parameters of reproductive performance or fetal toxicity. In rats treated with 2,4-dichlorophenol, the 30 ppm concentration decreased ($p \leq 0.10$) the number of pups surviving to weaning, and 300 ppm decreased ($p \leq 0.10$) litter size. A slight but not statistically significant increase in the number of stillborn pups was associated with all treatment levels of 2,4-dichlorophenol.

Rodwell et al. (1984) observed no increase in the incidence of teratological malformation in pups of F344 rats given 200, 375 or 750 mg/kg/day 2,4-dichlorophenol in corn oil by gavage throughout organogenesis. Maternal toxicity, manifested as a statistically significant and dose-related inhibition of maternal weight gain, was observed in all treated groups. Fetotoxic effects were observed in the high-dose group only and included reduced fetal body weight and a slight increase in early embryonic death.

3.3.2. Inhalation. Pertinent data regarding the reproductive effects of either 2-chlorophenol or 2,4-dichlorophenol after inhalation exposure could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

There were no pertinent data located in the available literature regarding toxicant interactions of either 2-chlorophenol or 2,4-dichlorophenol. The U.S. EPA (1980a,b) speculated that since both compounds are weak uncouplers of oxidative phosphorylation, concomitant exposure to other uncouplers may increase the severity of metabolic disorders.

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding human oral exposure to either 2-chlorophenol or 2,4-dichlorophenol could not be located in the available literature.

4.1.2. Inhalation. An occupational study of 4459 workers exposed to 2,4-dichlorophenol and 4-chloro-o-cresol based phenoxy herbicides, in addition to other pesticides and chemical intermediates, was conducted by Lynge (1985). In male workers, significant increases in relative risk ratios for lung cancer, rectal cancer and soft tissue sarcomas were reported; for females, there were increases in the relative risk of cervical cancer. Lynge (1985) considered only the soft tissue sarcoma incidence to be of significance, because it was also found to be elevated in several other occupational studies (Cook, 1981; Honchar and Halperin, 1981) involving exposure to phenoxy herbicides. In addition to the problem of exposure to a mixture of chemicals, the small cohort sizes in all of these studies obscures the significance of the findings.

4.2. BIOASSAYS

4.2.1. Oral. Exon and Koller (1985) exposed Sprague-Dawley rats to 0, 5, 50 or 500 ppm 2-chlorophenol, or 0, 3, 30 or 300 ppm 2,4-dichlorophenol in drinking water for ~2 years (see Section 3.2.1.). The dams of treated rats were exposed from 3 weeks of age through breeding, parturition and lactation, and the offspring were maintained on the same schedule until death or 24 months of age. Between 24 and 32 offspring/sex were used at each treatment level. Microscopic examination of major organs did not reveal increased tumor incidences, decreased latency to tumor formation or variations in tumor types, compared with control rates, in either 2-chlorophenol or 2,4-dichlorophenol-treated rats.

4.2.2. Inhalation. Pertinent data regarding the carcinogenic potency of either 2-chlorophenol or 2,4-dichlorophenol after inhalation exposure in experimental animals could not be located in the available literature.

4.3. OTHER RELEVANT DATA

Exon and Koller (1985) studied the potential synergistic effects of the human carcinogen, ethylnitrosourea, with each of the chlorophenols. Rat dams were orally exposed to ethylnitrosourea as the precursor ethylurea in the diet and sodium nitrite in the drinking water during gestation. Offspring were exposed, starting either prenatally or postnatally, to drinking water containing either 2-chlorophenol or 2,4-dichlorophenol for <24 months (see Section 4.2.). The investigators stated that tumor incidence increased, and time-to-tumor latency decreased, in all groups of male rats exposed both pre- and postnatally to 2-chlorophenol, compared with those exposed to ethylnitrosourea alone. These conclusions are tentative, however, because of the high tumor incidence in offspring exposed to ethylnitrosourea only and the lack of a concentration-response relationship. No synergistic effects were observed in female rats exposed to ethylnitrosourea and 2-chlorophenol, or in rats of either sex exposed to ethylnitrosourea and 2,4-dichlorophenol. The authors suggested that 2-chlorophenol may be a promotor or cocarcinogen with ethylnitrosourea.

Boutwell and Bosch (1959) found that 20% 2-chlorophenol, when applied as a promotor in 12- to 15-week skin-painting studies, with or without an initiator, led to papilloma formation in mice. Similar results were obtained with 2,4-dichlorophenol in 15- to 24-week studies. A total of 62% of survivors given 0.3% DMBA as an initiator and 2,4-dichlorophenol as a promotor had skin carcinomas 15 weeks after cessation of treatment. The U.S. EPA (1980a) criticized these studies on several grounds, including the

severe irritation caused by the high concentration, and the reporting of only gross pathological results. Moreover, the U.S. EPA (1979b) noted that, in the 2-chlorophenol studies, a solvent control group was not included.

With or without metabolic activation, 2-chlorophenol did not induce reverse mutations in Salmonella typhimurium (Haworth et al., 1983). The effects of 2,4-dichlorophenol on this test system were equivocal.

Amer and Ali (1968, 1969) found effects of 2,4-dichlorophenol on mitosis and meiosis in the vetch Vicia faba. The U.S. EPA (1980b) observed that the relationship of these changes to mutagenicity in mammalian cells was unclear.

4.4. WEIGHT OF EVIDENCE

Exon and Koller (1985) found that neither 2-chlorophenol nor 2,4-dichlorophenol act as complete carcinogens, although 2-chlorophenol may act as a cocarcinogen in male rats. These studies used inadequate sample sizes, which makes definitive conclusions difficult. In the occupational exposure studies (Lynge, 1985), it was unclear which herbicide intermediates were responsible for the increased relative risk of soft tissue sarcomas although chlorophenols were always present. Assays for reverse mutation (Haworth et al., 1983) indicate that neither compound is strongly genotoxic in bacterial cells.

The Exon and Koller (1985) studies with 2-chlorophenol and 2,4-dichlorophenol should be considered inadequate for assessment of risk of human carcinogenicity. 2-Chlorophenol and 2,4-dichlorophenol should be classified in EPA Group D (i.e., inadequate evidence of carcinogenicity in animals) (U.S. EPA, 1986b) or IARC Group 3 (i.e., cannot be classified as to their carcinogenicity in humans). However, while available evidence is inadequate for 2- and 2,4-chlorophenol, the related chlorophenals 2,4-D and 2,4,6-T are known carcinogens.

5. REGULATORY STANDARDS AND CRITERIA

The U.S. EPA (1980a,b) determined ambient water quality criteria of 0.1 µg/ℓ for 2-chlorophenol and 0.3 µg/ℓ for 2,4-dichlorophenol, based upon organoleptic (taste threshold) data provided by Dietz and Traud (1978).

An RfD_0 for 2,4-dichlorophenol of 0.003 mg/kg/day was derived based on a NOAEL for altered immune function of 3 ppm in the drinking water of rats exposed prenatally and for an additional 15 weeks (Exon and Koller, 1985; U.S. EPA, 1986c). An equivalent dose of 0.3 mg/kg/day was obtained assuming that daily water intake of rats is equivalent to 10% of their body weight. Using an uncertainty factor of 100 (10 for interspecies differences and 10 for individual differences), an RfD_0 of 0.003 mg/kg/day or 0.2 mg/day was derived for humans. Since the test animals were exposed both in utero and through milk before 15-week administration in drinking water, an additional factor for use of a subchronic study was not considered necessary (U.S. EPA, 1986c).

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). Subchronic toxicity studies with 2-chlorophenol in which adequate parameters of toxicity were evaluated could not be located in the available literature. A NOAEL of 50 ppm in drinking water for reproductive effects (Exon and Koller, 1982) and a NOAEL of 500 ppm for effects or measurements of immune functions (Exon and Koller, 1985) were identified in short-term studies using rats. An RfD_{SO} of 0.005 mg/kg/day for 2-chlorophenol can be calculated from a NOAEL of 50 ppm in drinking water in the reproduction study by Exon and Koller (1982). In this study, rats were exposed pre- and postnatally up to weaning age, and parameters were evaluated on reproduction including decreased litter sizes and number of stillborn. In the derivation of the RfD_{SO}, the NOAEL of 50 ppm in drinking water was transformed to an equivalent dose of 5 mg/kg/day based on the assumption that rats drink water equivalent to 10% of their body weight/day. In spite of the serious limitations in the parameters of toxicity evaluated in these studies, this RfD is adopted as the RfD_0 for 2-chlorophenol. Because little confidence can be placed in this data base, the RfD_0 of 0.005 mg/kg/day (0.35 mg/day) is adopted as the RfD_{SO}.

Subchronic studies with 2,4-dichlorophenol include a 6-month dietary study using mice (Kobayashi et al., 1972) in which 2000 ppm (100 mg/kg/day) was a NOAEL for histological effects on the liver and a short-term study using rats in which 30 ppm in the drinking water was a NOAEL for effects on measures of immune function (Exon and Koller, 1985). An RfD of 0.003 mg/kg/day for 2,4-dichlorophenol was derived by applying an uncertainty factor of 1000 to the dosage (0.3 mg/kg/day) estimated for the 3 ppm drinking water concentration NOAEL. The RfD, expressed as 0.02 mg/day for a 70 kg human,

was adopted as the RfD_0 for 2,4-dichlorophenol. Because the uncertainty factor of 100 is appropriate for derivation of an RfD_{SO} from subchronic data, the RfD_{SO} for 2,4-dichlorophenol is 0.2 mg/day.

6.1.2. Inhalation (RfD_{SI}). The lack of data regarding subchronic inhalation exposure to 2-chlorophenol or 2,4-dichlorophenol precludes derivation of RfD_{SI} values.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). An RfD for 2-chlorophenol of 0.005 mg/kg/day is derived from the oral subchronic reproduction and hematology NOAEL of 50 ppm in the short-term drinking water rat study by Exon and Koller (1982). Assuming that rats drink water equivalent to 10% of their body weight/day, the U.S. EPA (1986a) estimated an intake of 5 mg/kg/day associated with the concentration of 2-chlorophenol in drinking water. Application of an uncertainty factor of 1000 (10 for individual variability, 10 for interspecies differences, and 10 for use of subchronic study) resulted in the RfD of 0.005 mg/kg/day, or 0.35 mg/day for a 70 kg human, which is adopted as the RfD_0 for 2-chlorophenol.

Although a longer-term carcinogenicity experiment with 2-chlorophenol in rats has been performed more recently (Exon and Koller, 1985), adequate parameters of toxicity were not evaluated and this study is not useful for risk assessment. In another short-term experiment (Exon and Koller, 1985), prenatal and postnatal exposure to 2-chlorophenol at 5, 50 and 500 ppm in the drinking water had no adverse effects on measurements of immune function in rats. Because few parameters of toxicity were evaluated in these studies, little confidence can be placed on the data base from which the RfD_0 for exposure to 2-chlorophenol is derived.

An RfD_0 of 0.003 mg/kg/day for 2,4-dichlorophenol can be derived from the NOAEL of 3 ppm in drinking water for effects on measurements of immune functions in rats (Exon and Koller, 1985). Depressed cell mediated immune function was observed at 30 ppm, the higher concentration tested. The 3 ppm level is equivalent to 0.3 mg/kg/day when assumption is made that rats daily water intake is 10% of their body weight. This value was substantially below the NOAEL for liver changes in mice observed by Kobayashi et al. (1972). An uncertainty factor of 100 was applied resulting in the RfD of 0.003 mg/kg/day, or 0.02 mg/day for a 70 kg human (U.S. EPA, 1986d), which is adopted as the RfD_0 for 2,4-dichlorophenol.

Although in an earlier analysis, the U.S. EPA (1983a) did not have sufficient data to calculate a CS for 2-chlorophenol, the Exon and Koller (1982) reproductive study can be used for CS derivation. Repeated exposure of dams to 500 ppm (39 mg/kg/day, assuming rats drink 0.049 ℓ of water/day and weigh 0.35 kg) of 2-chlorophenol in drinking water led to small decreases in litter size and a slight increase in the number of stillbirths. Multiplication of the animal dosage by the cube root of the ratio of the rat body weight to the reference human body weight [assumed to be 0.35/70 kg (U.S. EPA, 1980d)], and again by 70 kg, results in a human MED of 469 mg/day. This MED corresponds to an RV_d of 1.3. Multiplication of the RV_d by an RV_e of 8 (for slight fetotoxicity) results in a CS of 10.4 for 2-chlorophenol and RQ of 1000.

The U.S. EPA (1983b) determined a CS of 11.9 for 2,4-dichlorophenol, based upon minor histopathological changes in mice (Kobayashi et al., 1972). A summary of this derivation is provided in Table 6-1.

Alternatively, the decrease in litter size observed in rats at 300 ppm by Exon and Koller (1985) suggests an effect level at 300 ppm. Using current methodology (U.S. EPA, 1984) and assuming rats weigh 0.35 kg and

TABLE 6-1

Composite Scores for the Toxicity of 2,4-Dichlorophenol by Oral Exposure

Species/ Strain	Sex	Exposure Dosage	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Mice/ICR	M	2000 ppm in diet for for 6 months (230 mg/kg/day)[a]	121[b]	2.38	reversible hepatic changes	5	11.9	1000	Kobayashi et al., 1972; U.S. EPA, 1983b
Rat/ Sprague-Dawley	F	300 mg/ℓ in drinking water from weaning at 3 weeks of age through mating at ~90 days of age through parturition (42 mg/kg/day)	503	1.4	decrease in litter size	8	11.2	1000	Exon and Koller, 1985

[a]Intake data provided by investigators

[b]Uncertainty factor of 10 applied to expand to chronic exposure

drink 0.049 ℓ of water/day, the concentration of 300 ppm corresponds to an intake of 42 mg/kg/day, associated with a human MED of 503 mg/day. The MED corresponds to an RV_d of 1.4. The effect of slightly increased fetotoxicity corresponds to an RV_e of 8. Multiplying the RV_d by the RV_e results in a CS of 11.2 for 2,4-dichlorophenol and an RQ of 1000.

The CS based upon the hepatic changes in mice (Kobayashi et al., 1972) is recommended to represent the toxicity of 2,4-dichlorophenol, since it is the higher of the two CSs calculated for 2,4-dichlorophenol.

6.2.2. Inhalation (RfD_I). The lack of pertinent data regarding the toxicity of 2-chlorophenol or 2,4-dichlorophenol after chronic inhalation exposure precludes derivation of RfD_I values.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Neither 2-chlorophenol nor 2,4-dichlorophenol was found to be carcinogenic when administered for 2 years in drinking water (Exon and Koller, 1985); however, 2-chlorophenol may have acted synergistically with ethylnitrosourea in inducing tumors in male rats (Exon and Koller, 1985). In both experiments, the lack of significantly increased tumor incidences precludes assessment of the carcinogenic potency of either compound.

6.3.2. Inhalation. Occupational studies (Lynge, 1985; Cook, 1981; Honchar and Halperin, 1981) involving exposure to phenoxy-based herbicides have suggested increased incidences of soft tissue sarcoma in exposed workers; however, lack of definition of the chemicals used and small cohort sizes, obscure the significance of these findings. In the absence of pertinent data from animal studies, assessment of risk from inhalation exposure to 2-chlorophenols or 2,4-dichlorophenol cannot be performed.

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APPENDIX A

Summary Table for 2-Chlorophenol[a]

	Species	Experimental Dose/Exposure	Effect	Reference Dose (RfD or RfD_S)
Oral				
RfD_{SO} (formerly AIS)	rats	50 ppm in drinking water from weaning through delivery of first litter (5 mg/kg/day)[b]	NOAEL for effects on reproduction	0.35 mg/day
RfD_O (formerly AIC)	rats	50 ppm in drinking water from weaning through delivery of first litter (5 mg/kg/day)[b]	NOAEL for effects on reproduction	0.35 mg/day
Maximum CS	rats	500 ppm in drinking water from weaning through delivery of first litter (39 mg/kg/day)[c] (RV_d=1.3)[d]	decreased litter size; increase number of stillborn (RV_e=8)	10.4

[a]Source: Exon and Koller, 1982

[b]In the calculation of this dose, U.S. EPA (1986a) assumed rats drink water equivalent to 10% of its body weight daily

[c]Assumed rats drink 0.049 ℓ water/day and weigh 0.35 kg (U.S. EPA, 1985b)

[d]Assumed body weight of reference man = 70 kg

APPENDIX B

Summary Table for 2,4-Dichlorophenol

	Species	Experimental Dose/Exposure	Effect	Reference Dose (RfD or RfD_S)	Reference
Oral RfD_{SO} (formerly AIS)	rats	3 ppm in drinking water, prenatal through 12-15 weeks post-weaning (3 mg/kg/day)[a]	NOAEL for effects on immune function	0.2 mg/day	Exon and Koller, 1982
RfD_O (formerly AIC)	rats	3 ppm in drinking water, prenatal through 12-15 weeks post-weaning (3 mg/kg/day)[a]	NOAEL for effects on immune function	0.2 mg/day	Exon and Koller, 1982
Maximum CS	mice	2000 ppm in diet for 6 months (230 mg/kg/day)[b] (RV_d=2.38)[c,d]	mild histological lesions in the liver (RV_e=5)	11.9	Kobayashi et al., 1972; U.S. EPA, 1983b

[a]In the calculation of this dose, it is assumed that rats drink water equivalent to 10% of their body weight daily

[b]Intake data provided by investigators

[c]Assumed reference body weight of mice = 0.03 kg; human = 70 kg

[d]Uncertainty factor of 10 applied to expand to chronic exposure